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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HALVORSON, MARK	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,503	HAMILL ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1-19, 24, 25, 28 and 31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-23,26,27,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-34 are pending.

Election/Restrictions

Applicant's election of Group 5 in the reply filed on October 20, 2008 is acknowledged. Applicant's election of the species antibody that binds to an epitope present on SEQ ID NO:6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 24, 25, 28 and 31-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species.

Claims 20-23, 26, 27, 29 and 30 are under examination.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 15, line 2. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code or replace the term "www" with "world wide web" or some other term. See MPEP § 608.01.

Claim Objections

Claim 29 objected to because of the following informalities: The word "pancreatic" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-23, 26, 27, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method for treating cancer, decreasing metastasis of a cancer and decreasing a symptom associated with cancer comprising administering to a subject having cancer an effective amount of a composition comprising amiloride that decreases activity of a mechanosensitive ion channel present on a cancer cell, does not reasonably provide enablement for method for treating cancer, decreasing metastasis of a cancer and decreasing a symptom associated with cancer comprising administering to a subject having cancer an effective amount of a composition comprising an agent that decreases activity of a MscCa channel, wherein the mechanosensitive channel is a mechanosensitive Ca-permeable channel (MscCa) wherein the agent is an antibody that specifically binds to an epitope present on SEQ ID NO:6, wherein the cancer is prostate cancer, breast cancer, colon cancer lung cancer, ovary cancer, pancreatic cancer or skin cancer, wherein the antibody decreases activity of an MscCa channel.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a method for treating cancer, decreasing metastasis of a cancer and decreasing a symptom associated with cancer comprising administering to a

subject having cancer an effective amount of a composition comprising an agent that decreases activity of a mechanosensitive ion channel present on a cancer cell, wherein the mechanosensitive channel is a mechanosensitive Ca-permeable channel (MscCa) wherein the agent is an antibody that specifically binds to an epitope present on SEQ ID NO:6, wherein the cancer is prostate cancer, breast cancer, colon cancer lung cancer, ovary cancer, pancreatic cancer or skin cancer, wherein the antibody decreases activity of an MscCa channel comprising a polypeptide comprising SEQ ID NO:2. The polypeptide comprising SEQ ID NO:2 which includes the epitope present on SEQ ID NO:6, is the MscCa channel protein, TRPC1.

The specification discloses that the MscCa channel is involved in the migration of a prostate cancer cell line. (Example 3). The specification discloses that inhibitors of the MscCa channel, including an antibody to the MscCa channel, TRPC1, inhibited Ca flux and the migration of a prostate cell line in vitro (Examples 4 and 5). The specification also discloses that the migration of the prostate cancer cell line was inhibited by an siRNA molecule to TRPC1 transfected into the prostate cancer cell line (Example 6). The specification does not demonstrate the ability of any MscCa inhibitor, including antibodies to the MscCa channel TRPC1, to inhibit cancer growth or metastasis in vivo.

It is well known that the art of anti-cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.)

With regards to the treatment of cancer with antibodies, White et al (Annu Rev Med 52:125-145, 2001) discloses that despite monoclonal antibody testing since the mid-1900's only in the past three years have some monoclonal antibodies provided sufficient efficacy as therapeutic agents (see Abstract). According to White et al, "The use of monoclonal antibodies for the treatment of carcinoma and hematologic

malignancies is an evolving field". (see Conclusion). White et al discloses that numerous obstacles must be overcome for successful immunotherapy. These include choice of target antigen, immunogenicity of the antibodies, length of half-life and ability to recruit effector functions and antibody manufacturing.

Additionally, Young et al. (US Patent Application Pub. 20040180002, September 15, 2004) teach that there have been many clinical trials of monoclonal antibodies for solid tumors. In the 1980s there were at least 4 clinical trials for human breast cancer which produced only 1 responder from at least 47 patients using antibodies against specific antigens or based on tissue selectivity. Young et al. teach that It was not until 1998 that there was a successful clinical trial using a humanized anti-her 2 antibody in combination with cisplatin (para 0010 of the published application). The same was true in clinical trials investigating colorectal cancer with antibodies against glycoprotein and glycolipid targets, wherein the specification specifically teaches that "to date there has not been an antibody that has been effective for colorectal cancer. Likewise there have been equally poor results for lung, brain, ovarian, pancreatic, prostate and stomach cancers" (para 0011 of the published application). Thus, it is clear that the art and the specification recognize that it could not be predicted, nor would it be expected that based only on the *in vitro* data presented in the specification that it would be more likely than not that the claimed antibody or variations of the antibody claimed could be effectively used for the treatment of any cancer. Although the tumor which was used to stimulate production of the claimed antibody clearly expresses the antigen, it is clear as set forth above, that it cannot be predicted, even when antigen is expressed that the claimed antibody would be effective for treating any cancer.

Furthermore, those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in- vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot

easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

In addition, Zips et al (In Vivo, 2005, 19:1-7).state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and, thereby drug access to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. **Therefore, prediction of drug effects in**

cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential."

With regards to the importance of the MscCa channel, TRPC1, in cancer, Gottlieb et al (Pflugers Arch, 2008, 455:1097-1103) discloses that the functional importance of TRPC1 in mammalian cells is unknown. (page 1097, 1st column), Dietrich et al (Pflugers Arch, 2007, 455:465-477) disclose that TRPC1 knockout mice have no apparent phenotype, having MscCa activity similar to that found in wild type mice. (page 476, 1st column). Gottlieb et al questions the specific role of TRPC1 in MscCa activity. (page 1098, 1st column). Furthermore, Verrall et al (Cancer Lett, 1999, 145:79-83 IDS) disclose that gadolinium, an inhibitor of the MscCa channel, increases the migration of prostate cancer cells. (Fig 1).

One cannot extrapolate the teaching of the specification to the enablement of the claims because the specification does not provide examples or guidance for treating any cancer in vivo with an inhibitor of the MscCa channel including an antibody to TRPC1. The specification only demonstrates that inhibitors of the MscCa channel, including an antibody to TSPC1, inhibit the migration of a prostate cancer cell line in vitro. The specification does not provide a nexus between the inhibition of the prostate cancer cell line in vitro with inhibitors of the MscCa channel, including the antibody to TRPC1, and the ability of inhibitors of the MscCa channel, including an antibody to TSPC1, to treat cancer, inhibit metastasis and decrease symptoms associated with cancer in vivo.

The art indicates the unpredictability in treating cancer including the treatment of cancer with antibodies. The art also discloses that in vitro results are not a good indicator of in vivo activity. In addition, it is unclear how the ability to inhibit the migration of a prostate cancer cell line in vitro correlates with the treatment of any cancer in vivo. Furthermore, the art indicates that even today the role of TRPC1 in mammalian cells is unclear.

Given the disclosure of the specification that discloses only in vitro results, and the teaching in the art that indicates the unpredictability of treating cancer with

antibodies, one skilled in the art could not predictably treat cancer in vivo with inhibitors of the MscCa channel, including antibodies to TRPC1.

Therefore, in view of the breadth of the claims, lack of guidance in the specification, the absence of working examples, and the state of the art, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Evans et al, (US Patent No: 6, 214, 824, issued April 10, 2001) as evidenced by Du et al. (Urology, 2007, 69:590-595 .

The claims are drawn to a method for treating cancer, decreasing metastasis of a cancer and decreasing a symptom associated with cancer comprising administering to a subject having cancer an effective amount of a composition comprising an agent that decreases activity of a mechanosensitive ion channel present on a cancer cell.

Evan et al discloses a method of treating cancer comprising administering to the host an amount of amiloride. (claim 1). As evidence by Du et al amiloride inhibits the activity of the mechanosensitive channel, ENaC (page 594, 2nd column to page 595, 1st column).

Summary

No claims allowed.

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Mark Halvorson/
Examiner, Art Unit 1642